REMARKS

Upon entry of the present amendment, claims 1-7, 10, 13-15, and 18-26 will be pending, new claims 19-26 having been added and claims 8, 9, 11, 12, 16 and 17 canceled without prejudice. Claims 1-7, 13-15, and 19-26 are presently under examination. Claims 10 and 18 are withdrawn from examination as drawn to an unelected invention. New claims 19-26 are, like claims 1-7 and 13-15, drawn to antibody screening methods, so Applicant asks that they be examined in the present application. Claims 1, 2, 6 and 7 have been amended to specify a bacterial host and to clarify antecedent basis for the antigen mentioned in step (e); support for the amended claims is found, for example, in the specification at page 10, lines 31-35. Claims 5 and 15 are amended to clarify their intended scope; support for the amendments are found, for example, in the specification at page 6, lines 7-15 and page 14, lines 24-30. Support for new claims 19 and 20 is found, for example, in original claims 1 and 2 and in the specification at page 13, line 2, to page 14, line 23; support for new claims 21 and 24 is found, for example, in original claims 3 and 13 and in the specification at page 10, line 26, and page 13, lines 15-16; support for new claims 22 and 25 is found, for example, in the specification at page 13, lines 19-22; support for new claims 23 and 26 is found, for example, in original claims 5 and 15 and in the specification at page 14, lines 24-27. No new matter has been added. Entry of the above amendment and allowance of all pending claims in view of the remarks in this Response are respectfully requested.

Prior grounds for objection or rejection

Applicant thanks the Examiner for noting that the corrected figures have been entered, obviating the objection to the specification, and that the prior rejections of the claims for anticipation and/or obviousness have been withdrawn.

Claim rejections under 35 U.S.C. § 112, first paragraph: lack of enablement

The Office Action at pages 4-10 sets forth a new rejection of the claims for alleged lack of enablement. As Applicant understands it, the Examiner based this rejection on two grounds:

(1) the fact that claims 1 and 2 encompassed use of a phage library in any kind of host cell, including eukaryotic cells (see the Office action at pages 8-9); and

(2) the Examiner's concern that one would have to undertake undue experimentation to make the claimed invention work in bacterial cells, because heavy chain secreted at high levels into the periplasmic space might aggregate (see the Office Action at pages 9-10).

If Applicant has incorrectly interpreted the Office Action in either regard, or if there were additional bases for the rejection not embraced by either of those grounds, clarification is requested.

Applicant believes that the above amendment of independent claims 1 and 2 to specify that the host cells are bacterial host cells fully addresses and overcomes part (1) of the enablement rejection. These claims and their dependents now all involve use of phage libraries in bacterial host cells, as opposed to in "any" type of cell.[1]

Applicant respectfully traverses part (2) of the enablement rejection. An invention, as defined by the claims, is enabled where one of ordinary skill in the art can make and use it without resorting to undue experimentation. See, *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed.Cir.1988). All of the evidence must be considered, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP § 2164.01(a).

Contrary to the Examiner's assertion, one of skill in the art would be able to practice the screening method of the claims without undue experimentation. As the Examiner recognizes, high level expression of recombinant proteins in *E. coli*, can, under certain circumstances, result in the production of insoluble aggregates in the periplasm. However, the observation that recombinant proteins in *E. coli* can aggregate when expressed at high levels is largely irrelevant to a screening method, in which high level expression of individual library members is not needed. Use of phage libraries in bacterial hosts to screen for two-chain antibodies is well known in the art, so techniques for avoiding aggregation of the secreted chain—if it is ever an issue--are apparently known. See, for example, Griffiths *et al.*, *The EMBO Journal* 13:3245-3260 (1994), a copy of which is attached hereto as Exhibit A. Griffiths *et al.* describe a method

[1] Note that claims 4 and 14 always specified that the host is *E. coli*.

of screening for two-chain Fab fragment antibodies using phage libraries in bacteria. According to the abstract, the method permitted selection of phage displaying functional Fab antibodies containing both heavy and light chains. Presumably both the heavy chain and the light chain would have been secreted into the periplasmic space during this process (the light chain being fused to a phage coat protein); the fact that functional antibodies resulted from the process indicates that, if aggregation occurred at all, it was not to an extent that prevented the screening assay from working. In addition, Griffiths *et al.*'s introductory paragraph cites a number of prior publications that also purport to disclose methods of displaying antibody fragments on the surface of phage. Clearly, those of skill in the art knew how to carry out antibody phage display successfully, unimpeded by problems with aggregation.

The Examiner cites the Kipryanov reference as evidence that aggregation can be a problem. According to the Office action at pages 9-10,

> The prior art does not recognize bacterial cells, more specifically E. coli, as being capable of secreting antibody fragments absent the fragment being engineered to have a bacterial signal peptide. As reviewed by Kipriyanov et al. (Molec. Biol. 12: pp 173-201 (1999)) E. coli can express antibody fragments such as Fab, Fv and scFv into the periplasm. "Periplasmic expression has permitted the functional testing of a wide variety of antibody fragments with different antigen binding specificities. The antibody fragments are usually correctly processed in the periplasm, they contain intramolecular disulfide bonds and are soluble. However, the high-level expression of a recombinant protein with a bacterial signal sequence in E. coli often results in the accumulation of insoluble antibody fragments after transport to the periplasm, presumably via the aggregation of a folding intermediate" . . . and "high protein concentrations of the secreted antibody fragment in the periplasmic space would favor the formation of insoluble aggregates over correct folding."

It is unclear why the Examiner is concerned about problems that may occur with high-level expression of antibodies in bacteria. High-level expression is not needed in order to do screening of libraries to discover functional antibodies. The very text from page 190 of Kipryanov that is quoted in the above passage of the Office Action ("**Periplasmic expression has permitted the functional testing of a wide variety of antibody fragments with different antigen binding specificities. The antibody fragments are usually correctly processed in the periplasm, they contain intramolecular disulfide bonds and are soluble.**") shows that Kipryanov recognized that these methods work. Kipryanov also discusses antibody phage libraries more explicitly at

pages 181-185. Nowhere does he imply that the techniques don't work, whether because of aggregation in the periplasmic space or otherwise. In fact, at page 185, col. 1, Kipryanov explains that when the antibodies displayed by the phage contain two chains (Fabs or diabodies or dsFv), the necessary dimerization of the two chains takes place in the periplasmic space. At page 183, col. 1-2, Kipryanov declares phage display libraries of antibodies to be "an excellent system for selecting specific clones." Thus, far from supporting the rejection for lack of enablement, Kipryanov provides evidence that even by 1999, the art knew how to carry out successful screening assays that rely on secretion of antibody chains into the periplasm and their assembly into functional two-chain antibodies. The fact that, as Kipryanov goes on to note, high level expression of a recombinant protein in *E. coli* (*e.g.*, for large-scale production of a desired antibody) may result in aggregation is irrelevant to the question of whether lower levels that are adequate for screening purposes would work. Kipryanov is certainly not saying that the potential for aggregation in the periplasm means that the art does not know how to carry out phage display of antibody libraries—far from it. Thus, the enablement rejection of the claims specifying use of bacterial host cells is not warranted and should be withdrawn.

Applicant notes that new claims 19-26 encompass use of eukaryotic host cells. These new claims do not recite use of phage libraries: instead, the library specified in step (b) of claims 19 and 20 is an expression vector library. Use of expression vector libraries in eukaryotic cells is standard in the art (see, *e.g.*, the publication WO95/15393 cited in the specification at page 13, line 2); their use in the context of the presently claimed methods is generally described in the specification at pages 13-14. Thus, there should be no enablement issues with respect to the new claims.

In view of the above, Applicant submits that the specification enables one of ordinary skill in the art, as of the effective filing date, to make and use the invention now claimed without resort to undue experimentation. Applicant contends that the present claims are in condition for allowance, which action is requested.

Please charge any required fees and apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 14875-0148US1.

Respectfully submitted,

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